Second International Cancer Chemoprevention Conference

This conference on cancer chemoprevention was designed to continue the international exchange of data and ideas from all disciplines of chemoprevention research begun during the first conference, which was held in 1990. The field of chemoprevention crosses many traditional research boundaries and includes research in epidemiology, statistics, clinical investigation, and molecular biology. The conference goal was to bring together leaders from several countries who work in this multidisciplinary field in order to disseminate new information and enhance continued research.

Covered at this second international conference was the status of clinical studies in the major cancer sites of lung, head and neck, colon, skin, and breast. The major new clinical data came from three randomized trials in patients with premalignant conditions; two of the trials studied oral leukoplakia, and one studied cervical dysplasia. These trials reported beneficial effects following treatment with retinoids. The large-scale Phase III trials discussed in 1990 are still ongoing. Much of the clinical discussion centered on trial methodology and the design of several new large-scale trials.

The most obvious difference between the two conferences was reflected in the tremendous increase in the understanding of epithelial carcinogenesis and mechanisms of retinoid action. Whereas these topics were only briefly presented in 1990, this conference featured elegant work from several groups of investigators describing the molecular biology of multistep carcinogenesis and field carcinogenesis, which are the central concepts of chemoprevention. Another important area of basic study presented here was the study of retinoid action. This work has already revealed that RAR-β3 plays a key role in aerodigestive tract carcinogenesis and retinoid chemoprevention. The laboratory work presented here provided a strong framework for chemopreventive drug development and study design.

The conference chairmen were Drs. Waun Ki Hong of The University of Texas M. D. Anderson Cancer Center, Houston, Texas, and Ugo Pastorino of the Istituto Nazionale Tumori, Milan, Italy.

Chemopreventive Agents and Mechanisms

The initial address of the conference was given by Dr. Michael B. Sporn (NCI, Bethesda, MD). Dr. Sporn began with the comment that the disease process in which chemoprevention should intervene is carcinogenesis. As a tumor progresses, it becomes increasingly heterogeneous and, perhaps, less amenable to regulation. Dr. Sporn reviewed the possible mechanisms through which retinoids may exert a chemopreventive effect. Retinoids interact with nuclear receptors in the retinoid/steroid superfamily. These receptors may exert an effect through the regulatory peptide, transforming growth factor-β, which is thought to be important in the control of epithelial proliferation. Not only retinoids but also vitamin D analogues may act through this mechanism.

The theme of retinoid receptors was continued in the presentation of Dr. Reuben Lotan (M. D. Anderson Cancer Center). Dr. Lotan reviewed the evidence that cell lines vary in their expression of retinoic acid receptors. Loss of RAR-β is associated with oral carcinogenesis. Treatment of oral premalignant lesions with 13-cis-retinoic acid has resulted in both regression of the lesions and increased expression of RAR-β.

Dr. Werner Bollag (Hoffman-LaRoche, Basel, Switzerland) discussed evidence of synergism between retinoids and cytokines in cell regulation. The interaction between retinoids and cytokines could be exploited in both cancer prevention and cancer treatment trials. Synergism in producing differentiation of HL-60 cells has also been observed with the combination of vitamin D and the retinoids 9-cis-retinoic acid or all-trans-retinoic acid.

Dr. Richard Moon (University of Illinois, Chicago, IL) emphasized that in order to both limit toxicity and increase efficacy, combinations of agents may be optimal for chemoprevention. He cited his work with animal models, such as the N-methyl-N-nitrosourea rat mammary carcinogenesis model in which the combination of 4-HPR and tamoxifen was synergistic.

Dr. Silvio DeFlora (University of Genoa, Genoa, Italy) discussed the potential cancer chemopreventive mechanisms of NAC. Possible mechanisms include detoxification of reactive compounds as an antioxidant, replenishment of glutathione stores, and inhibition of DNA adduct formation.

Dr. Gary Kelloff (NCI, Rockville, MD) discussed chemopreventive drug development. Chemoprevention agents in Phase II or III trials include retinol, 13-cis-retinoic acid, 4-HPR, calcium, β-carotene, tamoxifen, and finasteride. Dr. Kelloff also discussed some of the interesting agents undergoing Phase I trials such as 2-difluoro-methylnortin, sulindac, piroxicam, olitizapr, NAC, casboexolone, and β-glucyrhethinic acid. In addition to reviewing several chemopreventive agents under study, he discussed the strategy for developing biomarkers as end points for chemopreventive agent evaluation. He anticipates that, in the future, increased emphasis will be placed on cytomorphological abnormalities.

Dr. Winfred Malone (NCI, Bethesda, MD) presented information on a wide range of new agents being developed through the NCI. A synthetic analogue of the adrenal steroid dehydropiandrosterone (DHEA 8354) is about to begin Phase I clinical testing. Another agent in Phase I testing is carbenoxyolone, which is related to 18 β-glucyrhethinic acid. These Phase I clinical trials are needed to define the pharmacology and the dose required for a biological effect.

Intermediate Markers

Several presentations described efforts to define the process of carcinogenesis. Greater understanding of this process could lead to the development of intermediate markers, which could be used to guide chemoprevention trials. Since the goal of chemoprevention is to intervene before the development of clinically evident tumor, it would be extremely helpful to assess the impact of the agent without having to wait for the development of invasive disease. Studies designed to correlate the changes of carcinogenesis with clinical outcome due to the chemopreventive agent constitute an extremely active and exciting area of chemoprevention research.

Dr. Walter Hittelman (M. D. Anderson Cancer Center) discussed the work being done in his laboratory to define field carcinogenesis within the oral cavity. Polysomy, assessed using probes for chromosomes 7 and 17, increases within the field in association with the histological progression from normal-appearing epithelium to invasive cancer. The changes are not limited to the tumor, suggesting that damage from
Dr. Sabine Girod (University of Köln, Köln, Germany) assessed p53 expression using immunohistochemical techniques in tissue sections taken from patients with leukoplakia or squamous cell carcinoma of the oral cavity. Her results suggest that p53 expression increases with the progression from normal mucosa to invasive cancer. Increased p53 expression was associated with both loss of differentiation and increasing grades of dysplasia.

Dr. Marcel Copper (Free University Hospital, Amsterdam, the Netherlands) described the incorporation of intermediate marker studies into the large, Euroscan chemoprevention trial. Markers under evaluation include micronuclei, DNA content, and cytokeratin expression.

Dr. Gabriella Sozzi (Istituto Nazionale Tumori) presented results from a study comparing normal-appearing mucosa and tumor in 68 specimens resected from patients with lung cancer. Karyotype alterations were observed in 59% of the tumor specimens and 20% of the evaluable normal mucosa. Epithelial growth factor receptor was overexpressed in both the tumor (63%) and in normal mucosa (39%). The occurrence of these changes in both the tumor and the normal mucosa was statistically significant. The findings support the hypothesis of field carcinogenesis.

Dr. Pamela Rabbits (Medical Research Council Center, Cambridge, United Kingdom) discussed her work evaluating p53 mutations and chromosomal loss, especially —3p, in dysplastic lesions of the bronchial epithelium. Her results suggest that these abnormalities are frequently found in dysplastic epithelium. Identification of the chromosomal abnormalities associated with increased risk of developing cancer could be used for both early detection and prevention studies.

Dr. Charles Boone (NCI, Bethesda, MD) discussed the histological and biological characteristics of intraepithelial neoplasia. He described the use of specific, cytomorphological criteria to define the process of dysplasia and advocated the use of computer-assisted microscopy to quantitate these changes so that they may be used as chemoprevention trial end points.

Dr. J. Cloos (Free University Hospital) reported the results of her study using a mutagen sensitivity assay in which chromatic breaks were induced in cultured lymphocytes by bleomycin exposure. In this retrospective study, patients with squamous cell carcinomas of the head and neck had more chromosome breaks per cell than did normal controls (P < 0.001). The highest number of breaks per cell was observed in the patients who had developed multiple primary tumors.

Dr. Gian Paganelli (University of Bologna, Bologna, Italy) described the development of proliferation assays as intermediate biomarkers of colon cancer risk. Both PCNA and BrdUrd uptake were assessed in colon epithelium. Correlation was observed between these assays, although PCNA labeling was higher in the deeper crypt compartments than the BrdUrd labeling.

Dr. Harinder Garewal (Tucson VA Medical Center, Tucson, AZ) discussed the use of biological markers to assess the field defect in premalignant lesions of the stomach. Biopsy specimens from individuals with and without intestinal metaplasia were used to compare expression of BrdUrd labeling and ornithine decarboxylase. He found that ornithine decarboxylase levels were higher in individuals with intestinal metaplasia than in a control group, even if the biopsy specimens analyzed did not contain metaplasia.

Chemoprevention Trial Methodology

Dr. Thomas Pajak (American College of Radiology, Philadelphia, PA) discussed statistical issues in the design of chemoprevention studies. He emphasized the impact of compliance and loss of the preventive effect after cessation of the chemopreventive agent on the statistical power of a study. In chemoprevention trials to prevent SPTs, differences in the rates of SPTs due to the site of the initial tumor could also affect the study power. For chemoprevention trials, assumptions made to allow statistical calculations to guide the trial design may be performed over a decade before the study results are available.

Dr. John Baron (Dartmouth Medical School, Hanover, NH) discussed clinical issues in the conduct of chemoprevention trials. Evaluation of compliance must include not only individuals receiving active treatment but also the possibility of participants dropping in to the treatment, especially in trials of dietary substances. Difficulty in recruitment may also complicate the performance of these trials.

Dr. Peter Greenwald (NCI, Bethesda, MD) reviewed the NCI strategy for the conduction of large-scale chemoprevention trials. Dr. Greenwald discussed nine ongoing trials: the breast cancer prevention trial using tamoxifen; the prostate cancer prevention trial using finasteride; a trial in women studying vitamin E, β-carotene, and aspirin; a randomized trial of aspirin and β-carotene in U. S. physicians; a cancer prevention trial in persons with asbestosis using retinol and β-carotene; the Woman’s Health Trial Feasibility study; nutritional intervention studies of esophageal cancer in China; the large bowel adenomatous polyplex dietary intervention study; and a cancer prevention study in Finland using β-carotene and vitamin E.

Clinical Chemoprevention Trials

Dr. Michel Bolla (University of Grenoble, Grenoble, France) presented results of a double-blind trial of chemopreventive therapy performed following primary therapy for squamous cell carcinoma of the oral cavity or oropharynx. Patients were treated for 24 months with etretinate (25 mg/day) or placebo. In this study, no difference in the development of local-regional relapse or SPTs was observed.

Dr. Steven Benner (M. D. Anderson Cancer Center) presented results of a chemoprevention trial performed to determine whether 13-cis-retinoic acid could reverse bronchial squamous metaplasia and dysplasia in chronic smokers more effectively than placebo. Participants underwent bronchoscopy with endobronchial biopsies taken from six sites. There was no benefit associated with 13-cis-retinoic acid treatment compared with the placebo treatment; both treatment groups improved. Smoking cessation, however, was associated with a reduction in squamous metaplasia. Results of this randomized trial do not support the findings of earlier, uncontrolled studies.

Dr. Ugo Pastorino (Istituto Nazionale Tumori) reviewed lung cancer chemoprevention. Following resection of non-small cell lung cancer, treatment with retinyl palmitate (300,000 IU/day) was associated with a reduction of tobacco-related, new primary tumors. This trial served as the basis for the ongoing Euroscan study, which uses a 2 X 2 factorial design. Following therapy for an early-stage head and neck or non-small cell lung cancer, patients received NAC (600 mg/day), retinyl palmitate (300,000–150,000 IU/day), both drugs, or no treatment. Accrual for these trials is almost complete; nearly 2000 patients have been enrolled. Long-term follow-up of these patients will be necessary before the results of the intervention can be determined.

Dr. Nicoletta Tradati (Istituto Nazionale Tumori) presented interim results of an oral premalignancy chemoprevention study. Following surgical resection of a lesion, patients were treated with 4-HP (200 mg/day) or followed without further treatment. The drug has been well tolerated; no impaired dark adaptation has been observed. Of the 137 patients enrolled, 9 of 67 in the 4-HP group and 20 of 70 control group patients have developed recurrent leukoplakia.
Dr. Salvatore Toma (National Institute for Cancer Research, Genoa, Italy) reviewed the oral premalignancy studies performed by this group, including a trial with selenium. In a study with 18 evaluable patients, an overall response rate of 38.8% was observed. Toxic effects in this trial were very mild. In separate Phase II trials, responses were also observed with β-carotene and 13-cis-retinoic acid.

Dr. Scott Lippman (M. D. Anderson Cancer Center) discussed retinoid chemoprevention of oral premalignancy. In the most recent study, following induction therapy with a high dose of the drug, maintenance treatment with a low dose of 13-cis-retinoic acid prevented progression more effectively than did β-carotene. During the maintenance phase of the study, 8% (2 of 24 patients) in the 13-cis-retinoic acid group had progressive disease compared with 55% (16 of 29 patients) treated with β-carotene ($P < 0.001$). Dr. Lippman's current trial compares 3 years of therapy with a low dose of 13-cis-retinoic acid against the combination of retinyl palmitate and β-carotene.

Dr. Frank Meyskens (University of California at Irvine, Irvine, CA) presented results of a Phase III trial of trans-retinoic acid given to prevent progression of CIN. Participants included patients with moderate dysplasia (CIN II) or severe dysplasia (CIN III). Patients received three treatments of trans-retinoic acid or placebo, each treatment given topically over 4 days. Among the 160 participants with CIN III, no difference in response was observed; however, the topical retinoid was associated with a statistically significant improvement among the 141 participants with CIN II.

Dr. Trevor Powels (Royal Marsden Hospital, London, United Kingdom) described an ongoing trial of tamoxifen in preventing breast cancer. Over 1500 women with a family history of breast cancer have been enrolled. The agent has been well tolerated. Data being collected include cancer incidence, bone density, clotting factors, and lipids.

Dr. Larry Clark (University of Arizona, Tucson, AZ) reported on chemoprevention trials using selenium to prevent recurrence of adenomatous polyps in the colon and to prevent skin cancer. Dr. Clark is using the placebo treatment group to perform observational studies. In the placebo group of the colon chemoprevention trial, for example, he has observed an increase in polyp recurrence associated with lower plasma selenium levels when participants are grouped into quartiles.

**Concluding Session**

Following the presentation of papers, a session was held to discuss issues concerning future chemoprevention studies. The necessary duration of therapy remains controversial. Dr. Reuben Lotan cited data from animal models that suggest that long term administration of chemopreventive agents is necessary to maintain a protective effect. Dr. Frank Meyskens argued that it has not been shown clinically whether the same suppression of carcinogenesis may be achieved with shorter term administration of chemopreventive agents. Dr. James Mulshine (NCI, Rockville, Maryland) pointed out that agents now being tested, such as retinoids and tamoxifen, act to suppress rather than eliminate cancer.

Dr. Meyskens also cited the confusion concerning the meaning of the term “biomarker.” He suggested that it is now necessary to clarify what is meant by “biomarkers” and what standards may be used to assess them.

Dr. Bernard Weinstein (Columbia University, New York, NY) urged the participants to focus their efforts toward determining the causes of cancer. He suggested that interventions should examine both the process of carcinogenesis and the mechanisms of chemopreventive agents.

The conference provided an opportunity for a discussion of current chemoprevention research by an international group of participants. We hope this exchange will further the development of successful chemoprevention strategies.
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